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INTRODUCTION

The Frustrating Search for Schizophrenia Genes

The articles in this issue of Seminars in Medical Genetics motivate two strong, but somewhat paradoxical conclusions. A century of genetic epidemiologic research shows that genes play a substantial role in the etiology of schizophrenia. This is the only reasonable conclusion we can draw from the family, twin and adoption studies reviewed in this issue. On the other hand, molecular genetic studies, being contradictory, have frustrated efforts to find schizophrenia genes. Several chromosomal regions have been implicated by some studies, but none of these findings meet statistical criteria for significant linkage [Lander and Kruglyak, 1995]. Even more troublesome, the positive findings are offset by others that fail to implicate the same regions. Because consistent replication is a cornerstone of scientific inference, failures to replicate molecular genetic studies of schizophrenia might be interpreted to mean that schizophrenia genes do not exist.

That conclusion would be premature. Because twin and adoption studies suggest that the genetic contribution to schizophrenia is substantial, a more reasonable conclusion is that the genetic predisposition to schizophrenia is caused by multiple genes, each having a small effect. This conclusion is consistent with the pattern of risk to families, that suggests that several genes in epistasis lead to schizophrenia [Risch, 1990].

Notably, Suarez et al. [1994] showed that a pattern of some positive and some negative findings would be expected if a disorder were due to several susceptibility genes of small effect. In this situation, a pattern of replication and nonreplication would occur if the power to detect any specific gene was low but the power to detect one of a set was moderate to high. In this situation, any given study may detect one or two genes, but the power of other studies to replicate the result will be low unless they use a much larger sample.

This perspective suggests that, although the first phase of molecular genetic research in schizophrenia has not produced a schizophrenia gene, it has led to an important conclusion. We can now conclusively reject the idea that there is one gene of major effect that causes schizophrenia. Instead of searching for *the* schizophrenia gene, a second generation of genetic studies should be designed to detect the many genes of small effect that each increase susceptibility to the disorder. Because the technologies exist to find these genes, it is worthwhile to anticipate the future directions and clinical implications of what we now know—and what we will know—about the genetics of schizophrenia.

FUTURE DIRECTIONS

The most urgent need for molecular genetic studies of schizophrenia is to implement methods to improve the power to detect genes of small effect. One obvious alternative is to collect a very large sample of informative families. Because the National Institute of Mental Health has initiated a program to fund such research, we are likely to see compelling evidence for schizophrenia genes before too long.

But the statistical power of molecular genetic studies derives, not only from sample size, but also from the precision with which we define the phenotype being studied. It is well accepted that the development and use of relatively narrow diagnostic criteria over the last 25 years have improved our understanding of the epidemiology of schizophrenia, at least in part by stan-

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dardizing diagnostic criteria. For the purpose of conducting genetic studies, however, these diagnostic criteria may not be sufficient [e.g., Faraone et al., 1995].

We have suggested that diagnostic categories, along with their constituent symptoms, reflect relatively distal and variable effects of genes that increase vulnerability to schizophrenia [Tsuang et al., 1993]. In contrast, neurobiological dysfunctions may reflect relatively more proximal effects of such genes. The use of measures that are more closely related to individual schizophrenia genes would both reduce measurement error and increase the probability of replicating positive findings in linkage studies. This would be particularly true if minor genes for schizophrenia are major genes responsible for brain dysfunction. The use of this approach has yielded notable positive results in two paradigms. Schizophrenia linkage studies that incorporated eye-tracking [Arolt et al., 1996] and P50 evoked potential measures [Coon et al. 1993] as phenotypes, suggested linkage where the clinical diagnosis did not.

Ideally, we could perform molecular genetic studies, not on schizophrenia, but on some better measure of the genetic predisposition to schizophrenia. In 1962, Paul Meehl introduced the term "schizotaxia" to describe the genetic predisposition to schizophrenia [Meehl, 1962], which he thought resulted in a subtle, neural integrative defect. He proposed that schizotaxic individuals would eventually develop either schizotypy or schizophrenia, depending on environmental circumstances. Although schizotypy (in the form of schizotypal personality disorder) eventually entered the psychiatric nomenclature, schizotaxia did not. Instead, it became associated with the premorbid, neurobiological substrate of schizophrenia, but not with a clinically meaningful syndrome.

Now, after more than three decades of research, the accumulated evidence suggests that schizotaxia is, in fact, a marker for subsequent psychosis. As such, it encompasses aspects of both vulnerability and disease. In our reformulation of the concept, differences emerged from Meehl's original view. Although our use of the term remains consistent with Meehl's view of it as the underlying defect among people genetically predisposed to schizophrenia, it differs from his theory in at least three significant ways. First, unlike Meehl, we view the cause of schizotaxia as genetic and environmental, instead of only genetic. Second, we think the genetic cause of schizotaxia is best explained by a multifactorial, polygenic model, rather than by a single, major gene. Third, we do not view schizotypy or schizophrenia as the only, or even as the most common outcomes of schizotaxia.

It may seem odd to mention the environment in a discussion of genetic studies. Yet, better studies of environmental risk factors may improve our ability to find genes for schizophrenia. For example, statistical simulations by Khoury [1988] suggest that, in the presence of gene-environment interaction, the power to detect the effects of genes markedly improves if the environmental risk factor can be specified.

The case for environmental influence in schizophrenia/schizotaxia incorporates evidence from several sources. Notably, the risk of developing schizophrenia in a monozygotic twin (who shares 100% of his/her genes) whose co-twin develops schizophrenia is about 50%, which clearly implicates environmental agents in the cause of the disorder. Gottesman and Bertelsen [1989] showed that rates of schizophrenia in the offspring of identical twins who were discordant for schizophrenia were equal. These data suggest that individuals who possessed the schizophrenia genotype did not necessarily express the disorder. Moreover, there is a mounting body of evidence implicating two specific environmental risk factors in the cause of schizophrenia: obstetric complications [e.g., Geddes and Lawrie, 1995; Buka et al., 1999] and viral infections [e.g., Torrey and Kaufmann, 1986].

CLINICAL IMPLICATIONS

At this juncture, genetic studies of schizophrenia have not produced either markers for genetic counseling or gene-based therapies. Indeed, it is too soon to state if such developments will ever be possible [Faraone et al., 1999]. Eventually, however, the discovery of "schizophrenia" genes should lead to more effective treatments in three ways: pharmacogenomics, pharmacogenetics, and the identification of high risk children. Although each of these areas is still in its infancy, we can anticipate much progress after genes for schizophrenia are identified.

Pharmacogenomics uses known disease genes to develop new medicines. Given that the current efficacy of antipsychotic drug therapy is modest [Tsuang et al., 1999] and that these therapies are not based on the knowledge of schizophrenia's causal pathways, it is reasonable to suppose that medicines developed from a known causal pathway (implicated by molecular genetic studies) will be more efficacious. Although the success of this strategy has yet to be proved, it is currently being implemented by several biotechnology and pharmaceutical companies.

Pharmacogenetic studies show that genetic variation affects how people metabolize and respond to medicine. The use of pharmacogenetics for understanding metabolic differences is well known. These findings are well documented and available to practicing psychopharmacologists. What the future holds is the potential for pharmacogenetic data to guide the choice of drugs. Ideally, researchers would be able to show which specific genetic variants predict good and poor responses to specific agents for specific disorders. Pharmacogenetic data could also help determine which patients are at greatest risk for side effects. For example, although there are conflicting results, some studies suggest that abnormalities in genes for serotonin receptors may predict which schizophrenic patients show a good response to the atypical antipsychotic drug clozapine [e.g., Malhotra et al., 1996; Arranz et al., 1998].

The discovery of schizophrenia genes will also help us identify children at very high risk for the disorder, which will make it possible to develop and

implement early intervention strategies. At present, most early prevention programs emphasize secondary prevention, i.e., the early treatment and management of incipient psychotic symptoms [e.g., Falloon et al., 1996]. Although such programs are to be applauded, given the possibility that psychosis is toxic to the brain [Wyatt et al., 1996], treating schizotaxia—before the emergence of any signs of psychosis—may be another strategy for preventing schizophrenic psychosis.

Whereas the major clinical contributions of genetic research in schizophrenia may still be decades away, some benefits are evident already in the areas of genetic counseling, diagnosis and treatment [e.g., Moldin, 1997; Faraone et al., 1999]. Ideally, genetic counseling would be based on known genes, genetic markers, or risk figures from a model of genetic transmission. But such information is not yet available for schizophrenia. In its absence, family data must be used to make rough predictions. For example, it is reasonable to tell a schizophrenic patient that the risk to fraternal sibs for psychotic illness is about 10%.

Our understanding of schizophrenia as a familial disorder can also facilitate the diagnosis of the illness [e.g., Faraone et al., 1999]. For example, a psychiatric family history may be particularly helpful for "atypical" patients who are not clearly schizophrenic or mood disordered, or when little information about the patient is available. For example, if such an atypical patient had two bipolar sibs, a provisional diagnosis of bipolar disorder would certainly be in order. If these sibs were schizophrenic, the diagnosis of schizophrenia would prevail.

Finally, genetic research is relevant to the treatment of schizophrenia in at least three ways. First, if a patient has relatives with the disorder, their response to specific biological treatments may predict which medications will have optimal effects. Second, the genetic findings are relevant to medication compliance. The resistance of many schizophrenic patients to psychotropic medication is mitigated by discussing the biological and genetic etiology of the disorder. Third, genetic data are an important educational component to family counseling, to reduce the family's self-blame for the illness, to teach productive cooperation in the treatment of their relative(s), and to accept the necessity of medication.

SUMMARY

Although, as the papers in this special issue show, the search for schizophrenia genes has been frustrating, the field is slowly moving forward to address the many complexities of this disorder. By applying new methods of analysis and phenotype definition and by assessing key environmental risk factors, future studies are likely to clarify the genetic etiology and pathophysiology of schizophrenia. That in turn, should bring new tools to the armamentarium of the clinicians who must treat this devastating disorder.

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